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REVIEW

Association between phase angle and adverse clinical outcomes in hospitalized patients with COVID-19: A systematic review

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Abstract

Phase angle, obtained by bioelectrical impedance, is an indicator of cellular integrity and has been proposed as a prognostic parameter in patients who are critically ill. This systematic review aimed to evaluate the association between phase angle and adverse clinical outcomes in hospitalized patients with coronavirus disease–2019 (COVID-19). An extensive literature search was performed in the MEDLINE/PubMed, Embase, and Web of Science databases, with interest in observational studies evaluating the association between phase angle and adverse clinical outcomes in individuals aged ≥18 years hospitalized with COVID-19. Studies were independently selected by two reviewers, according to eligibility criteria. Subsequently, data were extracted and presented in a qualitative synthesis. The evaluation of the quality of the studies was performed according to the Newcastle-Ottawa scale. The full methodology was published in PROSPERO (ID CRD42022306177). A total of 392 articles were identified, resulting in seven selected studies, of which six were prospective cohorts and one was retrospective. In the quality assessment, six studies obtained scores equal to or greater than seven, indicating a low risk of bias. A total of 750 participants composed the samples of the selected studies. Five studies reported an independent association between phase angle and adverse clinical outcomes during hospitalization for COVID-19, with emphasis on prolonged hospitalization and mechanical ventilation and higher mortality in patients with a lower phase angle. Thus, phase angle measurement can be useful in the early identification of risks in patients hospitalized with COVID-19, for the purpose of adequacy of clinical management.

KEYWORDS
bioelectrical impedance, body composition, COVID-19, critical illness, length of stay, patient outcome, phase angle

INTRODUCTION

The coronavirus disease–2019 (COVID-19) pandemic has had a global socioeconomic impact, a high number of deaths,[1] and has been one of the main causes of hospital admissions.[2] According to data published by the World Health Organization (WHO),[3] until February 6, 2022, there were >392 million confirmed cases and >5.7 million deaths worldwide. This has triggered a rising interest in the identification of prognostic factors for mortality.

Studies have shown advanced age, male sex, and comorbidities such as cardiovascular disease, chronic obstructive pulmonary disease, and cancer are among the risk factors for severity and mortality of patients with COVID-19.[4–6] It is noteworthy that the severity of this disease can be divided into severe and critical conditions. In the latter, it is necessary to provide life-support therapies, such as mechanical ventilation (MV) and vasopressor therapy, due to the presence of acute respiratory distress syndrome, sepsis, septic shock, or other conditions of proportional severity.[7]

A meta-analysis including 42,219 individuals showed that patients with more severe cases of COVID-19 had an increased need for life-support interventions and high mortality (>30%).[8] These outcomes can be influenced by the nutrition status of the individual, as pointed out by a retrospective study in patients infected with severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2), in which patients who are critically ill at nutrition risk had a worse clinical outcome.[9]

Thus, it is interesting to assess the nutrition risk of these patients during early hospitalization.[10] A method of assessing nutrition status that can be conducted at the bedside, quickly and noninvasively, is the measurement of the phase angle (PhA), obtained through bioelectrical impedance analysis (BIA).[11,12] This parameter is calculated by the ratio between reactance (X_c) and resistance (R).[13] Most commonly, the PhA analysis is carried out at a frequency of 50 kHz.[11]

It is noteworthy that PhA reflects membrane integrity, cell mass, and hydration status, and is considered a biological marker of cell health.[14] For this reason, some studies have investigated the application of PhA as a prognostic indicator of severity during hospitalization. Low PhA values were inversely associated with length of stay (LOS),[12,15–17] length of intensive care unit (ICU) stay,[15,16,18] duration of MV,[15,16] and risk of mortality.[11,12,15,18]

However, the daily use of PhA in clinical practice has not been consolidated yet. In addition, its results may be affected by the hydration status, which is commonly altered in patients who are critically ill. Thus, it is necessary to expand studies on the predictive validity of PhA in critical illness in order to incorporate it into nutrition risk screening methods and other clinical outcomes.

To date, there is no systematic review published on the performance of PhA as a prognostic marker of morbidity and mortality in hospitalized patients with COVID-19. Thereby, this study can fill this gap by evaluating the use of this tool to screen individuals who are more susceptible to complications in order to support decisions in clinical management. Thus, the objective of this systematic review was to evaluate the association between PhA and adverse clinical outcomes in hospitalized patients with COVID-19.

METHODS

Protocol registration

The protocol of this systematic review entitled, "Association between phase angle and adverse clinical outcomes in hospitalized patients with COVID-19: a systematic review," followed the PRISMA guidelines for systematic review of the literature.[19] The full methodology was registered in PROSPERO on January 27, 2022, under protocol ID CRD42022306177.

Search strategy

A comprehensive search was performed in the MEDLINE/PubMed, Embase, and Web of Science databases on January 22, 2022, and was updated on February 20, 2022. In addition, a search was carried out in the gray literature, which included the access the BioRxiv preprint repository (www.biorxiv.org) and the Open Gray database (www.opengrey.eu). The patient, exposure, comparison, and outcomes strategy was used to define the guiding question of the study and the keywords.

Controlled search terms and their synonyms related to PhA and COVID-19 were used, with the following combination: (COVID-19 OR COVID 19 OR SARS-CoV-2 Infection OR 2019 Novel Coronavirus Infection) AND (Electric Impedance OR Impedance, Electric OR Electrical Impedance OR Impedance, Electrical OR Impedance OR Bioelectrical Impedance OR Impedance, Bioelectrical). There were no restrictions regarding language or year of publication.

Eligibility criteria

Eligible articles met the following inclusion criteria: (1) studies with volunteers aged ≥18 years, of both sexes,

and hospitalized with COVID-19; (2) observational studies that evaluated the association between PhA and adverse clinical outcomes of COVID-19; and (3) studies published in peer-reviewed journals. The exclusion criteria were (1) studies that did not meet the inclusion criteria; (2) reviews, meta-analyses, protocols, case reports, case series, editorials, and letter, to the editor; (3) studies with animal models; (4) studies with nutrition or drug interventions or with new therapies; and (5) studies with pregnant or lactating women.

Selection of studies

The files resulting from the search were uploaded to the Rayyan Systematic Review Online Data Management Platform[20] in order to exclude duplicate articles and perform the screening. Then, two reviewers (E.A.S.A and T.C.d.N.S.) independently performed the exclusion of articles in two stages: (1) after reading the title and abstract of each article; (2) after reading the articles selected in the previous step in full, to assess whether they met the eligibility criteria. In case of conflict of decision during the selection of articles, the reviewers decided by consensus. The reason for exclusion in the second stage was recorded.

Data extraction

Data from the selected articles were manually transferred into a Microsoft Excel spreadsheet, prepared by the authors, with the following information: first author's surname, year of publication, journal, country, study design, objective, sample characterization (number of participants, age, sex), bioelectrical impedance model and brand and protocol of use, PhA reference values and mean obtained in each study, comparative group, follow-up time, prespecified results, conclusions, and study limitations.

Risk of bias assessment

The evaluation of the methodological quality of the studies was performed using the Newcastle-Ottawa scale (NOS),[21] for cohort studies. In this eight-item scale, the measurement was calculated in three components: selection of groups (ranging from 0 to 4 points); comparability (ranging from 0 to 2 points) and exposure/result (ranging from 0 to 3 points), totaling 9 points as the maximum value. A score ≥7 was used as an indication of low risk of bias.

Data synthesis

A qualitative synthesis was performed to present the results of the studies. Data were summarized in structured tables, with grouping of similar information that allowed comparability, such as study design, sample characterization, bioelectrical impedance detail, main results, and conclusions.

RESULTS

Selected studies

A total of 392 articles were identified from the databases search (Figure 1). Of this total, 163 were removed due to duplication. After reading titles and abstracts, 218 articles were excluded. This resulted in 11 articles to be read in full and, of these, only 7 met the eligibility criteria.[22–28]

Quality of studies

Table 1 presents the result of the methodological quality assessment, according to the NOS for cohort studies, in which six articles obtained a score ≥7, indicating a low risk of bias.[22–24,26–28]

Characteristics of the studies

Of the seven observational studies included, six were prospective cohorts[22–24,26–28] and one was a retrospective cohort,[25] with a predominance of follow-up time of 60[24,28] and 90 days[23,27] since hospital admission. The period of publication of the studies was concentrated in the year 2021, with the exception of the Swiss study published in 2020[25] with the participation of 90 patients (Table 2).

A total of 750 participants composed the samples of the selected studies. The countries of origin were mostly European: two were conducted in the Netherlands,[22,23] one in Switzerland,[25] one in Italy,[28] and one in Spain.[27] Two other studies were carried out in Mexico[24,26] (Table 2). Only one study presented the population sample from more than one referral center[26] and only two articles mentioned the use of the sample size calculation.[24,27]

Regarding the age of the study participants, the mean and median >60 years prevailed. The lowest mean age observed was 54 ± 12 years in a study conducted in Mexico, which aimed to assess body composition and the presence of postextubation dysphagia.[26] The highest median age recorded was 69 years (59–80) in the study conducted in Spain, whose objective was to determine

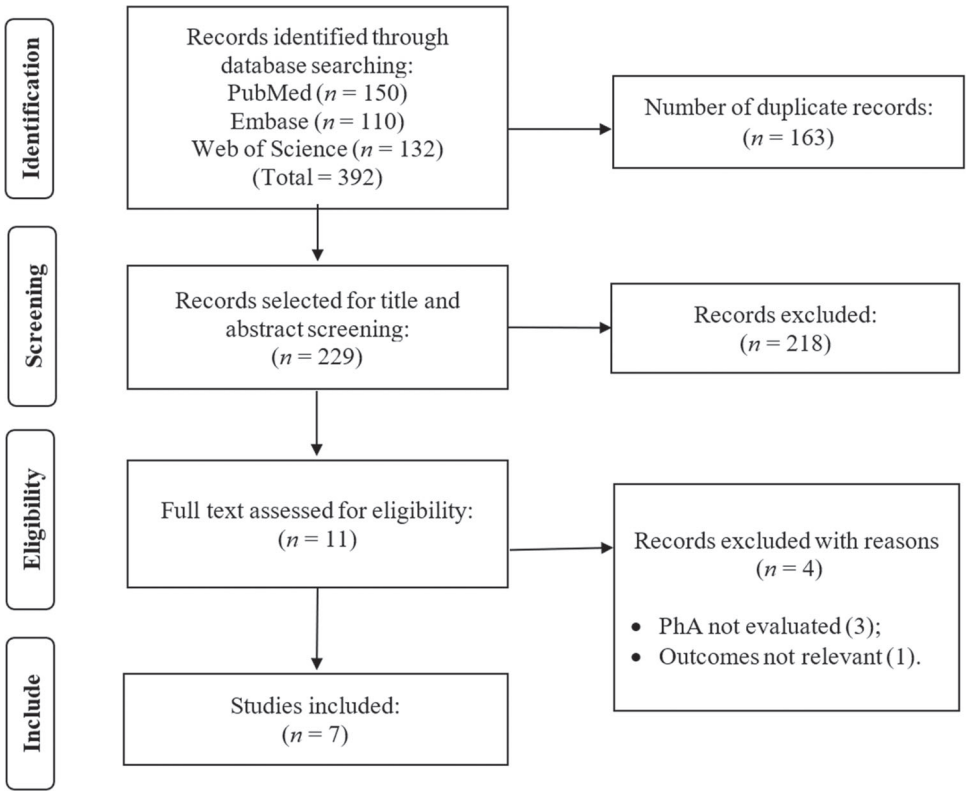

FIGURE 1 PRISMA search strategy flow diagram. PhA, phase angle.

TABLE 1 Risk of bias assessment according to the New Castle–Ottawa scale

Author, year	Selection	Comparability	Outcomes	Final score
Moonen et al., 2021[22]	3	1	3	7
Moonen et al., 2021[23]	3	2	3	8
Osuna-Padilla et al., 2021[24]	3	2	2	7
Del Giorno et al., 2020[25]	3	2	1	6
Reyes-Torres et al., 2021[26]	4	2	2	8
Cornejo-Pareja et al., 2021[27]	3	2	3	8
Da Porto et al., 2021[28]	3	2	2	7

the predictive value of PhA in the 90-day survival.[27] Regarding the sex of the participants, males predominated in all selected studies, with an average of 69.1%, as seen in Table 2.

Phase angle measurement

Regarding the bioelectrical impedance equipment, most studies[22–24,26] used the InBody S10® (InBody Co., Ltd.), a model that uses segmental impedance, reactance at multiple frequencies, and determines a whole-body PhA. Four out of the seven studies[22,23,26,27] analyzed the PhA at a frequency of 50 kHz, whereas three studies[24,25,28] did not disclose this information (Table 3). All studies analyzed the PhA with the patients in a supine position, whereas two studies[22,23] performed their measurements in a seated or supine position.

There was no uniformity regarding the moment of the BIA, varying from the first 24–72 h after hospital admission in most studies.[23,25,27,28] It is noteworthy that the study carried out in the Netherlands with 54 patients did not present predefined criteria for the measurement period[22] (Table 3).

TABLE 2 Characteristics of studies included in the systematic review

Author, year	Country	Study design	Participants	Age (years)	Sex	Follow-up time
Moonen et al., 2021[22]	Netherlands	Prospective cohort	54 ward and ICU patients	Mean: 67 (95% CI, 64–71)	63% male	28 days
Moonen et al., 2021[23]	Netherlands	Prospective cohort	150 ward and ICU patients	Mean: 68 (95% CI, 66–70)	67% male	90 days
Osuna-Padilla et al., 2021[24]	Mexico	Prospective cohort	67 patients who were critically ill	Mean: 55.3 (SD ± 13.6)	76% male	60 days
Del Giorno et al., 2020[25]	Switzerland	Retrospective cohort	90 ward patients	Mean: 64.5 (SD ± 13.7)	67.8% male	not reported
Reyes-Torres et al., 2021[26]	Mexico	Prospective cohort	112 patients discharged from the ICU	Mean: 54 (SD ± 12)	82% male	From extubation to ICU discharge
Cornejo-Pareja et al., 2021[27]	Spain	Prospective cohort	127 ward and ICU patients	Median: 69 (IQR: 59–80)	59.1% male	90 days
Da Porto et al., 2021[28]	Italy	Prospective cohort	150 ward patients	Mean: 69 (IQR: 58–78)	68.7% male	60 days

Abbreviations: ICU, intensive care unit; IQR, interquartile range.

Regarding the PhA values, the lowest median was observed in the study carried out in Spain, 4.4° (3.2°–5.4°),[27] whose median age was the highest among the studies. On the other hand, the highest PhA means were observed in studies with patients hospitalized exclusively in wards (5.6° ± 1.14°[25] and 5.5° ± 1.5°[28]). There were variations in the reference values of PhA adopted by the authors of the studies included in this review, with three studies showing average PhA below the reference values[22–24] (Table 3).

In addition, considering the fact that the PhA can be influenced by the volumetric state of the individual, four studies[22–24,26] highlighted the extracellular water/total body water ratio, as shown in Table 3.

Adverse clinical outcomes

The most evaluated clinical outcomes were LOS, MV, and mortality. The patients evaluated in the studies were allocated to comparative groups to carry out the effect measurements: ward and ICU[22,23]; survivors and nonsurvivors[24,27]; normal and at nutrition risk[25]; dysphagic and nondysphagic[26]; and no malnutrition and malnutrition[28] (Table 4).

Five studies (71.4% of selected articles) found an independent association between PhA and the presence of one or more adverse clinical outcomes during hospitalization for COVID-19.[22–24,26,27] The most commonly used association measures to assess the correlation between PhA and adverse clinical outcomes were odds ratio (OR) and hazard ratio (HR).

The highest OR obtained was 12.2 (95% CI, 4.3–34.1; $P < 0.05$) for the analysis of the association between PhA < 4.8° and postextubation dysphagia after adjustment for sex and age in the study[26] conducted with 112 patients. Regarding HR, the highest value presented was 3.912 (95% CI, 1.322–34.1; $P < 0.05$) in a prospective study with 127 patients, which evaluated the association between PhA and mortality risk during 90 days, in a model adjusted for sex, age, body mass index (BMI), comorbidities, and hydration status.[27] Thus, for every 1° decrease in the PhA value, there is a mortality risk ratio 3.9 times higher (Table 4).

Moreover, the study conducted in the Netherlands with 54 patients found that a higher PhA value was associated with a lower risk of mortality (OR = 0.208, $P = 0.025$).[22] On the other hand, the study with 67 patients who were critically ill[24] found an association between low PhA and a significantly increased risk of death (HR = 3.08; 95% CI, 1.12–8.41; $P = 0.02$), in an age-adjusted model and nutrition risk in the critically ill (NUTRIC) score. In contrast, the prospective

TABLE 3 Bioelectrical impedance analysis details reported in the studies included

Author, year	Model/brand	Frequency	Measurement period	PhA	PhA reference value	ECW/TBW	ECW/TBW reference value
Moonen et al., 2021[22]	InBody S10® (InBody Co., Ltd., Seoul, Korea)	50 kHz	No predefined criteria	4.5° (4.2°–4.8°)	Normal if = 5.6°–6.5°	0.40 (0.39–0.40)	0.36–0.39
Moonen et al., 2021[23]	InBody S10® (InBody Co., Ltd., Seoul, Korea)	50 kHz	24 h after hospital admission	5.4° (5.2°–5.6°)	Normal if = 5.6°–6.5°	0.39 (0.39–0.40)	0.36–0.39
Osuna-Padilla et al., 2021[24]	InBody S10® (InBody Co., Ltd., Seoul, Korea)	n/a	48 h after starting MV	−2.5° (−3.8°–0.83°)[a]	Standardized PhA[b] reduced if <−1.65	0.398 (±0.01)	n/a
Del Giorno et al., 2020[25]	BIA 101 (Akern Bioresearch®, Florence, Italy)	n/a	Up to 24 h after hospital admission	5.6° (±1.14°)	Bad nutrition if <4.3°	n/a	n/a
Reyes-Torres et al., 2021[26]	InBody S10® (InBody Co., Ltd., Seoul, Korea)	50 kHz	Upon discharge from the ICU	4.8° (±1.1°)	Low PhA if <4.8°	0.395 (±0.138)	>0.38: overhydration status
Cornejo-Pareja et al., 2021[27]	BIA 101 (Akern Bioresearch®, Florence, Italy)	50 kHz	Up to 72 h after hospital admission	4.4° (3.2°–5.4°)	n/a	n/a	n/a
Da Porto et al., 2021[28]	SECA®-model mBCA 525 (Seca GMBH & Co., Hamburg, Germany)	n/a	Up to 36 h after hospital admission	5.5° (±1.5°)	n/a	n/a	n/a

Abbreviations: BIA, bioelectrical impedance analysis; ECW, extracellular water; ICU, intensive care unit; MV, mechanical ventilation; n/a, not available; PhA, phase angle; TBW, total body water.

[a]Standardized PhA median.

[b]Standardized PhA equation: (measured PhA – mean of reference population PhA) ÷ SD of reference population.

TABLE 4 Main findings of studies included in the systematic review

Author, year	Comparative groups	Results	Conclusion
Moonen et al., 2021[22]	Ward and ICU patients	PhA and composite outcome score[a] (OR = 0.299, $P = 0.046$); PhA and mortality (adjusted OR = 0.208, $P = 0.025$).	Lower PhA increased the chances of severe COVID-19.
Moonen et al., 2021[23]	Ward and ICU patients	PhA and risk of ICU admission (OR = 0.531, $P = 0.021$), complications (OR = 0.579, $P = 0.031$), LOS (OR = 0.875, $P = 0.037$), and composite outcome[b] (adjusted OR = 0.502, $P = 0.012$).	PhA independently correlated with an adverse outcome from COVID-19.
Osuna-Padilla et al., 2021[24]	Survivors and nonsurvivors	PhA <3.85° in women (AUC = 0.83; 95% CI, 0.6–0.99) and <5.25° in men (AUC = 0.74, 95% CI, 0.6–0.88) in predicting mortality. PhA and 60-day mortality (adjusted HR = 3.08; 95% CI, 1.12–8.41; $P = 0.02$). PhA and LOS ($r = -0.33$, $P = 0.03$). PhA and duration of MV ($r = -0.42$, $P = 0.05$).	Low PhA values as a predictor of mortality in patients with COVID-19. PhA negatively correlated with LOS and MV.
Del Giorno et al., 2020[25]	Normal and at nutrition risk	PhA and prolonged hospitalization (adjusted OR = 1.04; 95% CI, 0.12–8.63; $P = 0.974$). PhA and LOS (adjusted $\beta = 4.77$; $P = 0.335$).	PhA does not appear to add a predictive value to COVID-19 clinical outcomes.
Reyes-Torres et al., 2021[26]	Dysphagic and nondysphagic	PhA <4.8° and postextubation dysphagia (adjusted OR = 12.2; 95% CI, 4.3–34.1; $P < 0.05$).	Lower PhA was an independent factor for postextubation dysphagia.
Cornejo-Pareja et al., 2021[27]	Survivors and nonsurvivors	PhA <3.95° as a predictor of mortality (AUC = 0.839; sensitivity, 93.8%; and specificity, 66.7%). PhA and risk of mortality (adjusted HR = 3.912; 95% CI, 1.322–11.572; $P = 0.014$).	Low PhA (<3.95°) is a significant independent predictor of mortality risk in COVID-19.
Da Porto et al., 2021[28]	No malnutrition and malnutrition	PhA and risk of death at 60 days (HR = 1.084, $P = 0.081$); PhA and need for invasive MV (adjusted HR = 1.007, $P = 0.007$).	PhA was not significantly associated with increased risk of death at 60 days.

Note: Statistical significance if $P < 0.05$.

Abbreviations: AUC, area under the curve; COVID-19, coronavirus disease–2019; HR, hazard ratio; ICU, intensive care unit; LOS, length of stay; MV, mechanical ventilation; OR, odds ratio; PhA, phase angle.

[a]Morbidity, ICU admission, and mortality.

[b]ICU admission, complications, and 90-day mortality.

study carried out in Italy with 150 patients found no association between PhA and risk of death at 60 days (HR = 1.084, $P = 0.081$) after adjusting for age, sex, and BMI[28] (Table 4).

As seen in Table 4, two studies used the receiver operating characteristic curve to assess the performance of PhA in predicting mortality. Thus, a PhA cutoff point of <3.95° was obtained to predict risk of death in 90 days in the Spanish study with 127 patients (area under the curve [AUC] = 0.839, $P = 0.001$), with a sensitivity of 93.8% and a specificity of 66, 7%.[27] In the study carried out with 67 patients who were critically ill, the predictive value of PhA for mortality was <5.25° in men (AUC = 0.74; 95% CI, 0.6–0.88) and <3.85° in women (AUC = 0.83; 95% CI, 0.6–0.99).[24]

Regarding LOS, a study with 150 ward and ICU patients found that greater PhA was associated with reduced hospital stay (OR = 0.875, $P = 0.037$), after adjusting for age, sex, and respiratory rate.[23] Similarly, the study with 67 patients who were critically ill showed a significant negative correlation between PhA and LOS ($r = -0.33$, $P = 0.03$).[24] On the other hand, the Swiss study did not observe a significant association ($\beta = 4.77$, $P = 0.335$) after adjusting for age, sex, BMI, comorbidities, serum glucose, and early warning score[25] (Table 4).

Two studies evaluated the performance of PhA in the correlation with MV (Table 4). In a prospective study with 67 patients who were critically ill followed up for 60 days[24]; the authors found that a lower PhA was related to a longer duration of MV ($r = -0.42$, $P = 0.005$). On the other hand, the Italian study with 150 general ward patients[28] did not show an association between PhA and the need for invasive MV, after adjusting for age, sex, and BMI (HR = 1.007, $P = 0.007$).

Study limitations

The limitations reported in the studies were (a) small sample size[22,24,25,27]; (b) data obtained from a single hospital center, which may compromise the generalization of the conclusions[25,27]; (c) cross-sectional nature of BIA measurements, which complicates interindividual comparability[22]; (d) different stages of the disease in the measurement period[27]; (e) inclusion of only ward patients, preventing expansion of the findings to other care modalities[28]; (f) infeasibility of body assessment at the time of patient admission[26]; and (g) intrinsic limitations of the retrospective design.[25]

DISCUSSION

In this systematic review, seven studies that investigated the association between PhA and adverse clinical outcomes of COVID-19 were evaluated. The results of five studies[22–24,26,27] demonstrated that lower PhA values were associated with worsening of the clinical condition of these patients, evidencing its potential as a predictor of adverse clinical outcomes. Similarly, the literature has shown that PhA can be used as a prognostic parameter in several clinical situations such as cancer,[15,17,29] heart failure,[30,31] kidney disease,[32,33] and HIV infection.[34,35]

Patients hospitalized with COVID-19 in the studies included were mostly male and aged over 60 years, corroborating with previous studies of clinical characterization of patients who were critically ill with COVID-19, because they pointed to advanced age and male sex as predictors of disease complications.[36–39]

The mean values of the PhA of the selected studies are in line with the results of other studies.[17,29,40,41] The highest PhA means were observed in studies with patients hospitalized exclusively in wards.[25,28] It should be noted that the studies included in this review presented different reference values for PhA analysis. However, to date, there is no precise value capable of identifying the prognostic performance in patients hospitalized with COVID-19. It is known that inflammation, malnutrition, and functional deficiencies can result in disturbances in the electrical properties of the tissue, consequently affecting the PhA.[42]

Another relevant aspect refers to the heterogeneity in the PhA measurement period, which can hinder the comparison of the results. This is due to the fact that, during critical illness, hydration markers can increase in the first 3 days of ICU stay, which leads to a reduction in PhA due to changes in reactance (marker of cell mass and integrity), as demonstrated in the prospective study with 156 patients conducted by Denneman et al.[43]

In this sense, three of the studies included in this review[24,25,27] took into consideration the results regarding total body water. The authors considered hydration status a confounding variable in their statistical analyses, in order to avoid a spurious association in the PhA assessment and interpretation.

Stapel et al.[14] stated that these changes in the patient's hydration status during ICU stay reflect inflammation-induced changes in membrane integrity, with consequent redistribution of fluid to the extracellular space and reduction of PhA. Thus, measuring PhA soon after admission is likely to reduce the confounding of altered hydration.

In addition, different confounding factors were considered for the adjustments in the statistical analyzes of the association between PhA and clinical outcomes during the hospitalization period. Pereira et al.[44] highlighted that these aspects should be considered in the study design when they involve PhA measures, as these confounding factors can lead to a loss in the associations between PhA and other variables.

The findings of this review confirm that PhA decreases with advancing age, in line with the results of other studies.[17,29,31,32] This is because of the loss of muscle mass and the gain of fat tissue, which can be attributed to the natural aging process.[45] It is worth mentioning that lean tissues are highly electrical current conductors, as they have a large amount of water and electrolytes. Therefore, they have low resistance to the passage of electric current. On the other hand, body fat has low conductivity and, as a result, high resistance,[46] which leads to a reduction in PhA.

When evaluating the relationship between PhA and mortality risk, three studies in this review[22,24,27] showed a significant and independent association. This result was also observed in a prospective study carried out with 134 cirrhotic patients, with a mean age of 54.3

years (±10.1), in which PhA values <4.9° significantly increased mortality (HR = 2.05; 95% CI, 1.1–3.77; $P = 0.021$).[47] PhA may, therefore, reflect a limited physiological reserve, which explains its association with mortality, influenced by both the acute disease and the underlying general condition.[14]

Corroborating with this finding, a study with 196 patients admitted to the ICU observed that individuals with PhA <4.8° had 3.7 higher risk of dying (OR = 3.65; 95% CI, 1.34–9.93; $P = 0.011$).[14] In another study with 241 patients who were critically ill, PhA values were also strongly associated with mortality outcomes (OR = 0.49; 95% CI, 0.35–0.66; $P = 0.0001$). The mean PhA in this sample was 4.0° (±1.4), with a significant difference between the surviving and nonsurviving groups (4.1° ± 1.3° vs 3.2° ± 1.5°, $P = 0.0001$).[11]

In contrast, a Brazilian study with 89 patients who were critically ill did not find a statistically significant difference between the PhA values of survivors and nonsurvivors (5.6° ± 1.1° vs 5.2° ± 2.2°, $P = 0.310$). In the multivariate analysis, there was no association between PhA < 5.5° and mortality (in crude: HR = 1.806; 95% CI, 0.888–3.676; $P = 0.103$; in adjusted: HR = 1.655, 95% CI; 0.772–3.544; $P = 0.195$).[41] However, it is worth noting that the PhA reference value adopted to assess the association with mortality was higher than those used in other studies.[14,18,30]

The Spanish study with 127 patients obtained the PhA cutoff point <3.95° to predict 90-day mortality in patients with COVID-19.[27] This value was lower than that found by Alves et al.[30] in a study with 71 patients with decompensated acute heart failure whose PhA value <4.8° (AUC = 0.726) was an independent factor for mortality (HR = 2.67, $P = 0.015$).

The association between PhA and LOS obtained in two studies in this review[23,24] was also reported in previous studies.[12,15,17] This association between lower PhA and worsening of the clinical condition of hospitalized patients may be related to membrane deterioration and cell death.[44,48] In patients who are critically ill, this reduction in PhA is caused by metabolic disorders, such as malnutrition and cachexia, in which the impaired nutrition status can result in an imbalance of body fluids and changes in the cell membrane.[44]

As for MV, the findings of the study with 67 patients who were critically ill[24] are in agreement with those of a prospective study carried out with critical cancer patients, in which it was observed that a lower PhA increased the duration of MV ($r = -0.428$, $P = 0.016$).[15] In another study with 50 patients undergoing cardiac surgery, PhA also showed a significant correlation with this variable ($P < 0.001$).[16]

This correlation between smaller PhA value and longer duration of MV may be related to sarcopenia, often found in patients who are critically ill, in which there is a reduction in the thickness of the diaphragmatic muscle. Acute declines in diaphragmatic muscle thickness can cause respiratory failure, contributing to the need for prolonged MV during hospitalization.[49] Thus, considering that sarcopenia is characterized by the loss of skeletal muscle mass and muscle function,[50] less electrical current conduction is expected, which implies greater resistance, therefore, a lower PhA value.

Implications for research

In view of the limited number of articles that evaluated the performance of PhA in predicting adverse clinical outcomes in patients hospitalized with COVID-19, it was not feasible to carry out a meta-analysis. For this reason, more primary studies on this subject should be conducted with the following specifications: prospective, multicenter, with a representative sample and use of a standardized protocol for PhA measurement obtained by the BIA.

We emphasize the importance of the PhA measurement period, preferably within the first 24 h of hospital admission, to avoid bias from the hydration status (commonly altered in patients who are critically ill) or the inclusion of this confounding variable in the adjusted model of the statistical analysis. In addition, randomized clinical trials may also be useful to investigate the effectiveness of clinical and/or nutrition interventions in patients with initially reduced PhA.

Implications for practice

In view of the results of the first studies that indicated PhA as an attractive parameter to assess the clinical progression of patients hospitalized with COVID-19,[22–24,26,27] we suggest the use of this marker as a complement to nutrition risk screening tools, after consolidating evidence in broader research.

Strengths and limitations

We highlight as strengths of this review, the search in different databases, with selection of articles from peer-reviewed journals. In addition, an assessment of the risk of bias of the selected studies was performed. This is the first systematic review that evaluates the association of

PhA and adverse clinical outcomes in hospitalized patients with COVID-19. As a limitation, we emphasize the impossibility of carrying out a meta-analysis due to the small number of studies that evaluated the performance of PhA in the morbidity and mortality of this target audience. In addition, we highlight as a limitation the heterogeneity of the populations regarding their health status (critically ill[22–24,26,27] and noncritically ill[25,28]).

CONCLUSION

The results of this review showed an independent association between PhA and the presence of one or more adverse clinical outcomes during hospitalization for COVID-19, with emphasis on prolonged LOS and duration of MV, as well as a higher risk of mortality in patients with lower PhA values. Thus, the findings of this systematic review suggest that this marker can be useful in identifying risk and monitoring during hospitalization, for the purpose of adapting clinical procedures.

AUTHOR CONTRIBUTIONS

Marcos Antonio Pereira dos Santos contributed to conception/design of the research; Elyudienne Andressa Silva Alves and Teresa Cristina do Nascimento Salazar contributed to acquisition, analysis, or interpretation of the data; Elyudienne Andressa Silva Alves drafted the manuscript; Valmir Oliveira Silvino, Glêbia Alexa Cardoso, and Marcos Antonio Pereira dos Santos critically revised the manuscript; Elyudienne Andressa Silva Alves, Teresa Cristina do Nascimento Salazar, Valmir Oliveira Silvino, Glêbia Alexa Cardoso, and Marcos Antonio Pereira dos Santos agree to be fully accountable for ensuring the integrity and accuracy of the work. All authors read and approved the final manuscript.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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